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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/245,615	02/04/1999	JAMES P. HOEFFLER	IVGN 274.1	5087

52059 7590 03/19/2008

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EXAMINER	
COOK, LISA V	
ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
03/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/245,615	HOEFFLER ET AL.	
	Examiner	Art Unit	
	LISA V. COOK	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-36,51,54,60-62,66,69-76 and 80-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-36,51,54,60-62,66,69-76 and 80-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicants' response to the Office Action mailed 6/18/07 is acknowledged (Paper filed 12/18/07). In the amendment filed therein claims 31 and 70 was modified. Claims 1-30, 37-50, 52-53, 55-59, 63-65, 67-68, and 77-79 have been canceled. Currently, claims 31-36, 51, 54, 60-62, 66, 69-76, and 80-83 are pending and under consideration.

2. Rejections and/or objections of record not reiterated below have been withdrawn.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

4. The information disclosure statements filed 12/18/07 has been considered as to the merits.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 70-73 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Shalon et al. (WO 95/35505).

Shalon et al. teach microarrays with immobilized reagents. The immobilized reagents include antibodies and antibody fragments that are dispensed on selected array positions. See abstract, page 11 lines 15-24, and page 31 lines 32-35, for example.

The discrete positions on the microarray are spaced apart (spatially addressable) on the solid support. See page 5 line 33, page 6 line 2, page 7 line 26-27. The source (cell line or cell type) of the antibodies at each discrete location is known. See page 12 line 32 through page 13 line 2.

In one embodiment, the microarray is treated to reduce non-specific binding with a polycationic polymer. See page 7 lines 30-32. The microarray has reagents (antibodies) spotted in discrete positions between 0.01 nanoliters and 100 nanoliters. See page 6 lines 8-10.

The microarray also comprises regions from 100 locations per square centimeter to 1000 locations per square centimeter. Page 12 lines 3-9. Shalon et al. further disclose that each region in the array contains an analyte specific reagent. It inherently teaches embodiments wherein a collection of 1000 different antibodies are provided on the microarray. See page 5 lines 26-29 for example. In considering the anticipatory effect of a reference, not only its specific teachings

but also the inferences which one skilled in the art would reasonably be expected to draw therefrom, should be taken into account. In re Preda (CCPA 1968) 401 F2d 825, 159 USPQ 342.

Response to Arguments

Applicants contend that the limitation with respect to a collection of 1000 different antibodies can read on each spot of the array containing one or more than one distinct antibody. See the response filed 12/18/07 - page 7, 1st paragraph. With Applicants arguments clarify that the antibody can read on 1000 spots comprising a single antibody and the amendment to claim 70 the limitation was reconsidered. Because Shalon et al. disclose that their microarrays comprises regions from 100 locations per square centimeter to 1000 locations per square centimeter (Page 12 lines 3-9) and further disclose that each region in the array contains an analyte specific reagent (Page 5 lines 26-29) for example; it inherently teaches embodiments wherein a collection of 1000 different antibodies are provided on the microarray. In considering the anticipatory effect of a reference, not only its specific teachings but also the inferences which one skilled in the art would reasonably be expected to draw therefrom, should be taken into account. In re Preda (CCPA 1968) 401 F2d 825, 159 USPQ 342. The rejection over Shalon et al. (WO 95/35505) is therefore maintained.

There is no "new ground" of rejection when the "basic thrust" of the rejection is the same. Ex parte Maas, 9 USPQ 2d 1746(Bd. Pat. App. & Int. 1987).

NEW GROUNDS OF REJECTIONS NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

II. Claims 31-33, 36, 51, 54, 60-61, 66, 69, 74-76, and 81-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879).

Please see Shalon et al. (WO 95/35505) as set forth above.

Shalon et al. differ from the instant invention in not specifically teaching a first and second fluorescent dye for labeling a cell lystate.

However, Unla et al. teach assay procedures to detect protein differences between two samples. The protein differences between two samples are evaluated in a modified 2-DE (two

dimensional polyacrylamide gel electrophoresis) technique called difference gel electrophoresis (DIGE). In particular, two protein samples are labeled with two cyanine dyes.

This allows for the simultaneous measurement of both samples on the same gel (array). Differences in the two samples due to differences in gene expression or protein modification can be identified quickly. See page 2071, 2nd column. In one embodiment *E. coli* transformed with the chimeric protein GAL4VP16 were induced for 15 min with IPTG. Extracts were labeled with either Cy3 or Cy5 and compared. See figure 4 on page 2076, for example.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to employ first and second fluorescent dyes as taught by Unla et al. with the microarray of Shalon et al. because Unla et al. taught that this allows for the simultaneous measurement of two samples (cell lists) on the same gel (array). Differences in the two samples due to differences in gene expression or protein modification can be identified quickly. See page 2071, 2nd column.

Shalon et al. in view of Unla et al. disclose the microarray and dual fluorescent dyes required by the claims. However, the references fail to teach kits. Kits are well known embodiments for assay reagents. Foster et al. (U.S. Patent #4,444,879) describe one example. In their patent kits including the reactant reagents, a microplate, positive controls, negative controls, standards, and instructions are taught. See figure 6, and column 15, lines 10-34.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to take the detection assay microarray and reagents as taught by Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and format them into a kit because Foster et al. teach that it is convenient to do so and one can

enhance sensitivity of a method by providing reagents as a kit. Further, the reagents in a kit are available in pre-measured amounts, which eliminate the variability that can occur when performing the assay.

Response to Arguments

Applicant's amendments and arguments that the cited references did not teach a first fluorescent reagent for labeling a cell lysate and a second fluorescent reagent for labeling a cell lysate, were carefully considered and found persuasive. Accordingly the reference to Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) has replaced Schuh et al. in the rejection.

Unla et al. teach assay procedures to detect protein differences between two samples. In particular, two protein samples (cell lists) are labeled with two cyanine dyes.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

While a deficiency in a reference may be overcome a rejection under 35 USC 103, a reference is not overcome by pointing out that a reference lacks a teaching for a which other references are relied. *In re Lyons*, 364 F.2d 1005, 150 USPQ 741, 746 (CCPA 1966).

III. Claims 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and

further in view of Foster et al. (U.S.Patent#4,444,879) as applied to claims 31-33, 36, 51, 54, 60-61, 74-76, and 81-83 above, and further in view of Ragg and Whitlow (FASEB, Vo1.9, January 1995, pages 73-80).

Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879) is set forth above.

Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879) differ from the instant invention in not teaching antibody fragments such as single chain/stranded recombinant antibody compositions.

However, Raag and Whitlow disclose single chain recombinant antibody fragments (sFv) consisting of only the variable light chain (VL) and variable heavy chain (VH) domains covalently linked by a polypeptide linker. Because the single chain recombinant antibody fragments are small they have rapid pharmacokinetics and tumor penetration in vivo. See abstract.

These single chain recombinant antibody fragments are derived from the antigen-binding domain of antibodies and are useful in any molecular recognition or binding application. See page 74 2nd column 2nd paragraph. SFv's are disclosed as tine reducers in ELISA applications. See page 74 2nd column middle of the 3rd paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use antibody fragments like recombinant single chain/stranded antibodies (sFv) as taught by Raag and Whitlow in the microarray of Shalon et al. (WO 95/35505) in view of Unla

et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879) to produce arrays to perform multiple sample analysis in the rapid detection systems because Raag and Whitlow taught that sFv's were small allowing for rapid penetration (abstract), useful in any antibody application (page 74 2nd column 2nd paragraph), and reduced time in ELISA procedures page 74 2nd column middle of the 3rd paragraph.

Response to Arguments

Applicant argues that Raag and Whitlow does not make up for the deficiencies of Shalon et al., Schuh et al., and Foster et al. This argument was carefully considered but not found persuasive because the combination of Shalon and Schuh has been modified and addressed *a priori*.

IV. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879) as applied to claims 31-33, 36, 51, 54, 60-61, 74-76, and 81-83 above, and further in view of Kohler et al. (Nature, 256, August 7, 1975, pages 495-497).

Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879) is set forth above.

Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879) differ from the instant invention in not teaching that the source of the antibodies is from a known hybridoma cell line.

However, Kohler et al. teach antibody production from a known hybridoma cell (tissue culture cell lines made from fused myeloma and spleen cells from an immunized donor). Kohler et al. disclose that the production of antibodies via hybridoma is a satisfactory source of monoclonal antibodies of predefined specificity.

The cells are versatile allowing for antibody production from different origins, can be grown in massive quantity, provide specific antibodies, and could prove valuable for medical and industrial utility. Page 495 1st paragraph and page 497 2nd column last paragraph. The specification teaches that the reference of Kohler et al. teaches hybridoma procedures on page 8 lines 13-19.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize hybridoma cells to produce antibodies as taught by Kohler et al. in the antibody microarray of Shalon et al. (WO 95/35505) in view of Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) and further in view of Foster et al. (U.S.Patent#4,444,879) because Kohler et al. taught that hybridoma cells are versatile allowing for antibody production from different origins, can be grown in massive quantity, provide specific antibodies, and could prove valuable for medical and industrial utility. Page 495 1st paragraph and page 497 2nd column last paragraph.

Response to Arguments

Applicant argues that Kohler does not make up for the deficiencies of Shalon et al., Schuh et al., and Foster. This argument was carefully considered but not found persuasive because the combination of Shalon and Schuh has been removed and addressed *a priori.*

7. For reasons aforementioned, no claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action.

In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week.

In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lisa V. Cook/
Examiner, Art Unit 1641

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641